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Display Date 8-12-02
Publication Date 8-13-02
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N–0400]

Agency Information Collection Activities; Submission for OMB Review; Comment Request; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995 (the PRA).

DATES: Submit written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Karen Nelson, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

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SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients—(OMB Control Number 0910–0392)—Reinstatement

FDA regulations require pediatric studies of certain new and marketed drugs and biological products to ensure that those products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval (see 63 FR 66632, December 2, 1998). Many drugs and biological products represent treatments that are the best available treatment for children, but most of them have not been adequately tested in the pediatric population. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. The regulations are intended to increase the number of drugs and biological products, with clinically significant use in children, that carry adequate labeling for use in that subpopulation. Specifically, the regulations are intended to address the following concerns: (1) Avoidable adverse drug reactions in children—drug reactions that occur because of the use of inadvertent drug overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due to the

physician's uncertainty about whether the drug or the dose was safe and effective in children.

The regulations contain the following reporting requirements that are subject to the PRA:

21 CFR 201.23(a)—Manufacturers of marketed drug products submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations; applicants develop a pediatric formulation for FDA approval.

21 CFR 201.23(c)—Applicants request a full waiver of the requirements under § 201.23(a) by certifying that necessary studies are impossible or highly impractical or there is evidence that the product would be ineffective or unsafe in all pediatric age groups. Applicants request a partial waiver of the requirements under § 201.23(a) by certifying that: (1) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, it is not likely to be used in a substantial number of patients in that age group, and the absence of adequate labeling could not pose significant risks to pediatric patients; or (2) necessary studies are impossible or highly impractical, or there is strong evidence that the product would be ineffective or unsafe in that age group, or the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

21 CFR 312.47(b)(1)(iv)—Sponsors submit background information on the sponsor's plan for phase 3, including plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies.

21 CFR 312.47(b)(2)—Sponsors submit information on the status of needed or ongoing pediatric studies.

21 CFR 314.50(d)(7)—Applicants submit a pediatric use section, describing the investigation of the drug for use in pediatric populations.

21 CFR 314.55(a)—Applications contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric subpopulations and to support dosing and administration.

21 CFR 314.55(b)—Applicants request a deferred submission of some or all assessments of safety and effectiveness required under § 314.55(a) by certifying to the grounds for delaying pediatric studies, a description of planned or ongoing studies, and evidence that studies will be conducted at the earliest possible time.

21 CFR 314.55(c)—Applicants request a full waiver of the requirements under § 314.55(a) by certifying that the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients, necessary studies are impossible or highly impractical, or there is strong evidence that the product would be ineffective or unsafe in all pediatric age groups. Applicants request a partial waiver of the requirements under § 314.55(a) by certifying that: (1) The product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group and it is not likely to be used in a substantial number of patients in that age group; (2) necessary studies are impossible or highly impractical; (3) there is evidence that the product would be ineffective or unsafe in that age group; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

21 CFR 314.81(b)(2)(i)—Applicant's annual report includes a brief summary of whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population have been initiated.

21 CFR 314.81(b)(2)(vi)(c)—Applicant's annual report includes an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.

21 CFR 314.81(b)(2)(vii)—Applicant's annual report includes a status report containing a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23, and if so, the status of these studies.

21 CFR 601.27(a)—Applications for new biological products contain data that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in pediatric subpopulations, and to support dosing and administration information.

21 CFR 601.27(b)—Applicants request a deferred submission of some or all assessments of safety and effectiveness required under § 601.27(a).

21 CFR 601.27(c)—Applicants request a full waiver of the requirements under § 601.27(a) by certifying that the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients, necessary studies are impossible or highly impractical, or there is strong evidence that the product would be ineffective or unsafe in all pediatric age groups. Applicants request a partial waiver of the requirements under § 601.27(a) by certifying that: (1) The product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age

group and it is not likely to be used in a substantial number of patients in that age group; (2) necessary studies are impossible or highly impractical; (3) there is evidence that the product would be ineffective or unsafe in that age group; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

21 CFR 601.28(a)—Sponsors annually submit to FDA a brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated.

21 CFR 601.28(b)—Sponsors submit to FDA an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.

21 CFR 601.28(c)—Sponsors submit to FDA a statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant.

FDA estimates that the collection of information resulting from these regulations is as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
201.23(a)	2	1	2	48	96
201.23(c)	0	0	0	0	0
312.47(b)(1)(iv)	107	1.2	131	16	2,096
312.47(b)(2)	100	1.3	127	16	2,032
314.50(d)(7) and 314.55(a)	59	1.3	78	50	3,900
314.55(b)	60	1.3	80	24	1,920
314.55(c)	79	1.3	105	8	840
314.81(b)(2)(i)	119	1.3	158	8	1,264
314.81(b)(2)(vi)(c)	119	1.3	158	24	3,792
314.81(b)(2)(vii)	6	1	6	1.5	9
601.27(a)	2	1	3	48	144
601.27(b)	5	1	5	24	120
601.27(c)	3	1	4	8	32
601.37(a)	69	1	69	8	552
601.37(b)	69	1	69	24	1,656
601.37(c)	69	1	69	1.5	104
Total					18,557

In the **Federal Register** of September 27, 2001 (66 FR 49389), FDA requested comments on the proposed collection of information. FDA received

one comment. The comment stated, generally, that FDA underestimated the resources required to satisfy the collection of information, and requested that the agency provide a more detailed discussion of the assumptions and methodology used to develop the estimates.

First, the comment stated that the burden to comply with the information collection requirements in § 201.23(a) "would involve hundreds of hours of development time and a variety of scientific specialities" if a sponsor had to submit a supplemental application or a new drug application (NDA) for a pediatric formulation. The comment said that even if the burden for submitting a pediatric application is included under the other estimates in the **Federal Register** notice (66 FR 49389), the burden for § 201.23(a) (which "would be limited to the sponsor's 'opportunity for a written response and a meeting which may include an advisory committee meeting'") would still be greater than the 48 hours per response estimated by FDA.

Second, the comment stated that FDA's estimate for compliance with the information collection requirements in §§ 314.55(a) and 601.27(a) is low "because the collection, analysis, and reporting of data adequate to support pediatric use of a new drug or biological product * * * involves extensive resources of a multidisciplinary team to plan and execute the necessary clinical development program * * *."

Third, the comment questioned why FDA's estimate for the number of annual responses in § 314.50(d)(7) is not equal to the estimate for the number of annual responses in § 314.55(a), because "§ 314.50(d)(7) requires the pediatric section of an application to include "information submitted under § 314.55."

Fourth, the comment questioned why FDA did not provide a burden estimate for § 314.50(d)(3) (human pharmacokinetics (PK) and bioavailability section of an application) and (d)(5) (clinical data section of an application).

Fifth, the comment stated that FDA's estimate of 100 respondents for § 314.81(b)(2)(i), (b)(2)(vi)(c), and (b)(2)(vii) is low, and that "FDA might expect approximately 3,000 responses annually" (not including responses from holders of approved biological license applications) because there are approximately 3,000 NDAs included in the *Approved Drug Products With Therapeutic Equivalence Evaluations*.

FDA appreciates the information provided by the comment and has reconsidered the burden estimates in the September 27, 2001, notice.

Concerning the question whether the numbers in table 1 (66 FR 49389 at 49390) represent totals of all submissions since December 2, 1998, or whether they represent an annualized number based on the total received, table 1 of this document contains annualized estimates based on the submissions received.

Concerning the comments on the adequacy of FDA's burden estimates for §§ 201.23(a) and 314.55(a), the agency agrees that the collection and analysis of data adequate to support pediatric use and to develop a pediatric formulation would be more burdensome than the estimates provided in the September 27, 2001, notice. The September 27, 2001, notice and this document, however, are part of the process to request that OMB extend approval for the collection of information described in the final rule entitled "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologicals Products in Pediatric Patients," published in the **Federal Register** of December 2, 1998 (63 FR 66632 at 66659). In the final rule

(63 FR 66632 at 66660), FDA also estimated the costs associated with conducting and analyzing efficacy studies, PK studies, and new dosage form development. These industry costs total approximately $80 million annually. The analysis of the economic impact of the regulation is required under Executive Order 12866, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act. The added burden cited by the comment for §§ 201.23(a) and 314.55(a) has been estimated by FDA in the economic analysis. Only the burden associated with compiling and reporting to FDA information already obtained is the subject of this notice and the September 27, 2001, notice. FDA published for public comment its initial estimate of this collection of information in the **Federal Register** of August 15, 1997 (62 FR 43900 at 43909). In the final rule, FDA discussed the comments on the burden estimates and revised the estimate for §§ 201.23(a) and 314.55(a) from 16 hours to 48 hours. Thus, FDA believes that the collection of information estimate together with the cost estimate made in the analysis of the economic impact of the regulation provide an adequate assessment of the industry burden resulting from §§ 201.23(a) and 314.55(a).

As a result of the comment that the number of annual responses in § 314.50(d)(7) should be equal to the number of annual responses in § 314.55(a), FDA has reconsidered its analysis of the collection of information resulting from these sections of the regulation. Under § 314.50(d)(7), applicants must submit as part of an application and supplement to an approved application a "pediatric use section." This section must describe the investigation of the drug for use in pediatric populations, including an integrated summary of the information that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for

the claimed indications, a reference to the full descriptions of such studies provided under § 314.50(d)(3) and (d)(5), and information required to be submitted under § 314.55. Under § 314.55(a), applications must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. FDA has determined that, for purposes of this collection of information analysis, the requirement to submit pediatric use information would more appropriately come under § 314.50(d)(7). Section § 314.55(a) is the requirement to obtain pediatric use information for reporting to FDA under § 314.50(d)(7). Thus, FDA is including the reference to § 314.55(a) in the same entry as § 314.50(d)(7) in table 1 of this document. As a result of more recent data, FDA has revised its estimate of the number of responses and respondents under § 314.50(d)(7). Based on the number of submissions to FDA of the required assessments of pediatric safety and effectiveness during 2001, FDA estimates that approximately 59 applicants will submit approximately 78 assessments annually.

Concerning the comment that FDA did not provide a burden estimate for § 314.50(d)(3) and (d)(5), this notice and the September 27, 2001, notice are part of the process to request that OMB extend approval for the collection of information described in the December 2, 1998, final rule. The final rule did not amend § 314.50(d)(3) and (d)(5) and, therefore, these sections were not included in the collection of information analysis in the final rule. The information collection under § 314.50(d)(3) and (d)(5), as well as other provisions under 21 CFR part 314, are already approved by OMB until November 30, 2004, under OMB control number 0910–0001.

The comment also stated that FDA's estimate of 100 respondents for § 314.81(b)(2)(i), (b)(2)(vi)(c), and (b)(2)(vii) is low, and that over 3,000 responses should be expected annually. Under these sections, applicants must submit in their annual report: (1) A brief summary of whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population have been initiated; (2) an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information; and (3) a status report containing a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23, and if so, the status of these studies. Thus, only the annual reports for those approved applications that contain or will contain pediatric use information would be covered by these sections. As a result of more recent data, FDA has revised its estimates of the number of responses and respondents for these sections. Based on the number of currently approved applications and the number of pending applications that contain pediatric use information, FDA estimates approximately 119 applicants will submit approximately 158 annual reports under § 314.81(b)(2)(i), approximately 119 applicants will submit approximately 158 annual reports under § 314.81(b)(2)(vi)(*c*), and approximately 6 applicants will submit approximately 6 annual reports under § 314.81(b)(2)(vii).

As a result of more recent FDA data on the number of requests for deferrals and waivers received by the agency in 2001, FDA has also revised the estimates for § 314.55(b) and (c) as reflected in the table 1 of this document.

Dated: 8-6-02

August 6, 2002.

Margaret M. Dotzel,
Associate Commissioner for Policy.

[FR Doc. 02–????? Filed ??–??–02; 8:45 am]

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